Mitochondrial Dysfunction in Embryonic Stem Cells

Grant Award Details

Mitochondrial Dysfunction in Embryonic Stem Cells

Grant Type: SEED Grant

Grant Number: RS1-00432

Investigator:

Name:	Vincent Procaccio
Institution:	University of California, Irvine
Type:	PI

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $245,582

Status: Closed

Grant Application Details

Application Title: Mitochondrial Dysfunction in Embryonic Stem Cells

Public Abstract: Mitochondrial Dysfunction in Embryonic Stem Cells {REDACTED} A major concern for the utilization of human Embryonic Stem Cells (hESCs) for cell replacement therapy is that with prolonged culture, the capacity of the cells to generate the desired cell types for therapy declines. While the reason for this is currently unknown, our research suggests that an important factor is damage to the genetic blueprints that are necessary to sustain the cellular power plants of the cell, the mitochondria. The human cell is the product of a symbiotic merger that occurred two billion years ago of two different cell types: one generating the host cell and the other generating an intra-cellular colony of bacteria, the mitochondria. In the modern human cell, the host cell constitutes the nucleus and the cytosol and the genetic information (DNA) for this nucleus-cytosol organism resides in the nucleus and is responsible to building and maintaining the structural elements of the cell: analogous to the carpenters blueprints for building a house. The mitochondria have their own DNA blueprints, the mitochondrial DNA (mtDNA), and this describes the circuit diagram for the energy production system of the mitochondria: analogous to the electrician's wiring diagram for the house. Mutations which damage the mtDNA circuit diagram result in the mitochondria's inability to repair damage to the mitochondrial energy production system. As the efficiency of the mitochondrial power plants declines, they make less energy and more smoke, the smoke generated being oxygen radicals. As oxygen radical production increases, it causes increased damage to the mitochondria and mtDNAs, ultimately resulting in the mitochondrial power plants go off-line and the death of the cell. As mitochondrial oxygen radical production increases, it stimulates the cell to divide in an effort to dilute out the smoke generating mitochondria. However, the problem is that the damaged mtDNA blueprints replicate along with the cell. Hence, the toxicity continues to increase. We and others have documented this type of phenomenon occurs in a variety of cultured cell types. Therefore, it is likely that it also occurs in hESCs. If so, as damage to the mtDNA accumulates, hESC energy production declines and oxygen radical production increases until the hESC is no longer capable of building the more complex structures necessary to create tissue replacement cells. If we can prove that this scenario does occur in hESCs, then we can develop drugs that will limit mitochondrial oxygen radical production and protect the mitochondria and mtDNAs from oxygen radical damage. Furthermore, we have developed a method that permits us to replace damaged mtDNAs in cells with new one. Hence we could repair the mtDNA damage of aging hESCs and regenerate their capacity to make high quality differentiated cells for use in tissue replacement therapy.

Statement of Benefit to California:	Prolonged cell culture of human Embryonic Stem Cells (hESCs) frequently results in the loss of the cell's capacity to differentiate on command into well differentiated cells. This eliminates their utility for generating replacement cells for use in cell replacement therapy to repair damaged tissues and organs within the body. The reason for this loss of developmental capacity by the hESCs is currently unclear, but we believe that a major factor contributing to the decline in the therapeutic value of hESCs is the accumulation of deleterious mutations in the mitochondrial DNA (mtDNA) of the cultured hESCs. The mtDNAs are located in the mitochondria which are organelles in the cytoplasm of the human cell. The mitochondria are responsible for generating most of the energy used by the cell and as a toxic by-product, the mitochondrial generate most of the endogenous reactive oxygen species (ROS). The mtDNA encodes key elements of the mitochondrial energy generating apparatus, and since ROS is a mutagen, the mtDNA is highly prone to acquiring mutations in these energy genes. These mutations then inhibit mitochondrial energy production which also results in increased ROS production. Increased mitochondrial ROS production stimulates the cell growth, so the cells with the mutant mtDNAs out grow the normal cells. However, the more rapidly growing cells with the mutant mtDNAs also have reduced mitochondrial energy production, which together with the increased ROS production, inhibits the developmental capacity of the hESC.In this research, we propose to establish that deleterious mtDNA mutations do in fact accumulate in hESCs over time and that they play an important role in the loss of the developmental potential of hESC cells. If we can confirm that this is a fact, then we should be able to greatly increase the therapeutic potential of hESCs by developing procedures for protecting the mtDNA of the hESCs from oxidative damage. This might be accomplished by growth of hESCs in the presence of mitochondrially target antioxidants. Furthermore, cells that had lost their developmental potential might be revitalized by simply replacing the damaged mtDNAs with good mtDNAs using our trans-mitochondrial cybrid technique.Thus, the proposed research has the potential of greatly increasing the therapeutic potential of all hESCs that will be developed in the State of California.